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(54) Title: pH-MODIFIED BIOCOMPATIBLE MONOMER AND POLYMER COMPOSITIONS

(57) Abstract

The pH-modified monomer and polymer compositions are useful as biomedical and surgical adhesives, sealants, implants and bioactive agent release carriers or matrices. They comprise a monomer or polymer; and an effective amount of an acidic or basic pH mofifier effective to modify the pH of an immediate *in vivo* environment of the composition to a pH range at which the polymer biodegrades at a different rate then at physiologic pH. The invention also relates to *in vivo* applications in which surfaces are joined or treated with such pH-modified biocompatible compositions.

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PH-MODIFIED BIOCOMPATIBLE MONOMER AND POLYMER COMPOSITIONS

Field of the Invention

This invention relates to improved compositions useful as biomedical adhesives, sealants, implants and bioactive agent release matrices. This invention also relates to medical, surgical and other *in vivo* applications in which body tissue surfaces are joined or reinforced with biocompatible compositions.

Background

The products in primary use for wound closure are surgical sutures and staples. Sutures are recognized to provide adequate wound support. However, sutures cause additional trauma to the wound site (by reason of the need for the needle and suture to pass through tissue) and are time-consuming to place, and, at skin level, can cause unattractive wound closure marks. Surgical staples have been developed to speed wound apposition. However, surgical staples also impose additional wound trauma and require the use of ancillary and often expensive devices for positioning and applying the staples.

To overcome these drawbacks, fast-acting surgical adhesives have been proposed. One group of such adhesives is the monomeric forms of alpha-cyanoacrylates.

Reference is made, for example, to U.S. Patents Nos. 3,527,841 (Wicker et al.); 3,722,599 (Robertson et al.); 3,995,641 (Kronenthal et al.); and 3,940,362 (Overhults), which disclose that alpha-cyanoacrylates are useful as surgical adhesives. All of the foregoing references are hereby incorporated by reference herein.

Typically, when used as adhesives and sealants, cyanoacrylates are applied in monomeric form to the surfaces to be joined or sealed, where, typically, *in situ* anionic polymerization of the monomer occurs, giving rise to the desired adhesive bond or seal. Implants, such as rods, meshes, screws, and plates, may also be formed of cyanoacrylate polymers, formed typically by radical-initiated polymerization.

However, a drawback to the *in vivo* biomedical use of alpha-cyanoacrylate monomers and polymers has been their potential for causing adverse tissue response. For example, methyl alpha-cyanoacrylate has been reported to cause tissue inflammation at the site of application.

The adverse tissue response to alpha-cyanoacrylates appears to be caused by the products released during *in vivo* biodegradation of the polymerized alpha-cyanoacrylates. It is believed that formaldehyde is the biodegradation product most responsible for the adverse tissue response and, specifically, the high concentration of formaldehyde produced during rapid polymer biodegradation. Reference is made, for example, to F. Leonard et al., *Journal of Applied Polymer Science*, Vol. 10, pp. 259-272 (1966); F. Leonard, *Annals New York Academy of Sciences*, Vol. 146, pp. 203-213 (1968); Tseng, Yin-Chao, et al., *Journal of Applied Biomaterials*, Vol. 1, pp. 111-119 (1990), and to Tseng, Yin-Chao, et al., *Journal of Biomedical Materials Research*, Vol. 24, pp. 1355-1367 (1990), which are hereby incorporated by reference herein.

For these reasons, cyanoacrylates have not come into widespread use for biomedical purposes.

Efforts to increase the tissue compatibility of alpha-cyanoacrylates have included modifying the alkyl ester group. For example, increasing the alkyl ester chain length to form the higher cyanoacrylate analogues, e.g., butyl-2-cyanoacrylates and octyl-2-cyanoacrylates, has been found to improve biocompatibility but the higher analogues biodegrade at slower rates than the lower alkyl cyanoacrylates.

Other examples of modified alpha-cyanoacrylates used in biomedical applications include carbalkoxyalkyl alpha-cyanoacrylates (see, for example, U.S. Patent No. 3,995,641 to Kronenthal et al.), fluorocyanoacrylates (see, for example, U.S. Patent No. 3,722,599 to Robertson et al.), and alkoxyalkyl 2-cyanoacrylates (see, for example, U.S. Patent No. 3,559,652 to Banitt et al.). Other efforts have included mixing alpha-cyanoacrylates

with dimethyl methylenemalonate and higher esters of 2-cyanoacrylic acid (see, for example, U.S. Patent No. 3,591,676 to Hawkins et al.).

In other efforts to increase the usefulness of alpha-cyanoacrylate adhesive compositions for surgical applications, certain viscosity modifiers have been used in combination with alkyl alpha-cyanoacrylate monomers, such as methyl alpha-cyanoacrylate. See, for example, U.S. Patents Nos. 3,564,078 (wherein the viscosity modifier is poly(ethyl 2-cyanoacrylate)) and 3,527,841 (wherein the viscosity modifier is poly(lactic acid)), both patents being to Wicker et al.

In a related application, U.S.S.N. 08/040,618, filed March 31, 1993 (U.S. Patent 5,328,687), the entire contents of which are hereby incorporated by reference, the use of formaldehyde scavengers has been proposed to improve biocompatibility of alpha-cyanoacrylate polymers, whose biodegradation produces formaldehyde, for use in *in vivo* applications. It is known that various compounds can affect polymerization of alpha-cyanoacrylate monomers, including acids to inhibit or slow polymerization (e.g., Leonard et al., U.S. Patent 3,896,077), and bases to accelerate polymerization (e.g., Coover et al., U.S. Patent 3,759,264 and Dombroski et al., U.S. Patent 4,042,442).

SUMMARY OF THE INVENTION

It has not been known to regulate polymer biodegradation by regulating the pH of an immediate *in vivo* environment of a biocompatible composition. Such regulation would improve, for instance, the biocompatibility of 1,1-disubstituted ethylene polymers for *in vivo* applications, by controlling the rate of release of harmful byproducts (*e.g.*, formaldehyde) and controlling the rate of degradation of the polymer *in situ*.

Combining the monomer composition with a biocompatible pH modifier effective to regulate the pH of an immediate environment of the *in situ* polymer will substantially improve the usefulness of polymers formed

from such monomers, particularly in combination with use of formaldehyde scavengers.

The present invention is also directed to methods of using the above-described monomers, copolymers and polymers made therefrom for biomedical purposes.

The monomer compositions of this invention and polymers formed therefrom are useful as tissue adhesives, sealants for preventing bleeding or for covering open wounds, systems for delivery of therapeutic or other bioactive agents, and in other biomedical applications. They find uses in, for example, apposing surgically incised or traumatically lacerated tissues; setting fractured bone structures; retarding blood flow from wounds; aiding repair and regrowth of living tissue; and serving as matrices for delivering bioactive agents and as implants.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Embodiments of the present invention provide a biocompatible monomer composition, comprising an effective amount of at least one biocompatible pH modifier effective to regulate the pH of an immediate *in vivo* environment of the polymer to a pH range at which the polymer's *in vivo* biodegradation proceeds at a different rate than it does at physiologic pH.

In a further embodiment, the present invention is directed to a biocompatible composition comprising a polymer whose *in vivo* biodegradation may produce formaldehyde, and a pH modifier as described previously, and optionally including a formaldehyde scavenger.

The monomers used in this invention are polymerizable, e.g. anionically polymerizable or free radical polymerizable, to form polymers which biodegrade. In some embodiments, they form active formaldehyde upon biodegradation.

Monomer compositions of this invention may be applied to a surface to be sealed or joined together with a second surface *in vivo*, where, typically, *in situ*

anionic polymerization of the monomer occurs, giving rise to the desired adhesive bond or seal.

Useful 1,1-disubstituted ethylene monomers include, but are not limited to, monomers of the formula:

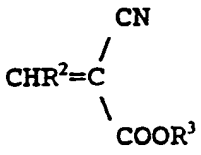
(I) $CHR=CXY$

wherein X and Y are each strong electron withdrawing groups, and R is H, $-CH=CH_2$ or, provided that X and Y are both cyano groups, a C_1-C_4 alkyl group.

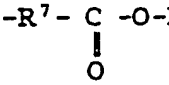
Examples of monomers within the scope of formula (I) include alpha-cyanoacrylates, vinylidene cyanides, C_1-C_4 alkyl homologues of vinylidene cyanides, dialkyl 2-methylene malonates, acylacrylonitriles, vinyl sulfinates and vinyl sulfonates of the formula $CH_2=CX'Y'$ wherein X' is $-SO_2R'$ or $-SO_3R'$ and Y' is -CN, $-COOR'$, $-COCH_3$, $-SO_2R'$ or $-SO_3R'$, and R' is H or hydrocarbyl.

Preferred monomers of formula (I) for use in this invention are alpha-cyanoacrylates. These monomers are known in the art and have the formula

(II)



wherein R^2 is hydrogen and R^3 is a hydrocarbyl or substituted hydrocarbyl group; a group having the formula $-R^4-O-R^5-O-R^6$, wherein R^4 is a 1,2-alkylene group having 2-4 carbon atoms, R^5 is an alkylene group having 2-4 carbon atoms, and R^6 is an alkyl group having 1-6 carbon atoms; or a group having the formula



, wherein R^7 is $-CH_2-$, $-\overset{CH_3}{\underset{|}{CH}}-$, or $-C(CH_3)_2-$, and R^8 is an organic radical.

Examples of suitable hydrocarbyl and substituted hydrocarbyl groups include straight chain or branched chain alkyl groups having 1-16 carbon atoms; straight chain or branched chain C_1-C_{16} alkyl groups substituted with an acyloxy group, a haloalkyl group, an alkoxy group, a halogen atom, a cyano group, or a haloalkyl group;

straight chain or branched chain alkenyl groups having 2 to 16 carbon atoms; straight chain or branched chain alkynyl groups having 2 to 12 carbon atoms; cycloalkyl groups; aralkyl groups; alkylaryl groups; and aryl groups.

In the cyanoacrylate monomer of formula (II), R^3 is preferably an alkyl group having 1-10 carbon atoms or a group having the formula $-AOR^9$, wherein A is a divalent straight or branched chain alkylene or oxyalkylene radical having 2-8 carbon atoms, and R^9 is a straight or branched alkyl radical having 1-8 carbon atoms.

Examples of groups represented by the formula $-AOR^9$ include 1-methoxy-2-propyl, 2-butoxyethyl, 2-isopropoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxybutyl.

Especially advantageous alpha-cyanoacrylate monomers for use in this invention are methyl alpha-cyanoacrylate, butyl alpha-cyanoacrylate, 2-octyl alpha-cyanoacrylate, 1-methoxy-2-propyl cyanoacrylate, 2-butoxyethyl cyanoacrylate, 2-isopropoxyethyl cyanoacrylate and 3-methoxybutyl cyanoacrylate. Equally advantageous are 2-methylene malonates, such as dimethyl 2-methylenemalonate.

The alpha-cyanoacrylates of formula (II) wherein R^3 is a hydrocarbyl or substituted hydrocarbyl group can be prepared according to methods known in the art. Reference is made, for example, to U.S. Patents Nos. 2,721,858 and 3,254,111, each of which is hereby incorporated by reference herein. For example, the alpha-cyanoacrylates can be prepared by reacting an alkyl cyanoacetate with formaldehyde in a non-aqueous organic solvent and in the presence of a basic catalyst, followed by pyrolysis of the anhydrous intermediate polymer in the presence of a polymerization inhibitor. The alpha-cyanoacrylate monomers prepared with low moisture content and essentially free of impurities are preferred for biomedical use.

The alpha-cyanoacrylates of formula (II) wherein R^3 is a group having the formula $-R^4-O-R^5-O-R^6$ can be

prepared according to the method disclosed in U.S. Patent No. 4,364,876 (Kimura et al.), which is hereby incorporated by reference herein. In the Kimura et al. method, the alpha-cyanoacrylates are prepared by producing a cyanoacetate by esterifying cyanoacetic acid with an alcohol or by transesterifying an alkyl cyanoacetate and an alcohol; condensing the cyanoacetate and formaldehyde or paraformaldehyde in the presence of a catalyst at a molar ratio of 0.5-1.5:1, preferably 0.8-1.2:1, to obtain a condensate; depolymerizing the condensation reaction mixture either directly or after removal of the condensation catalyst to yield crude cyanoacrylate; and distilling the crude cyanoacrylate to form a high purity cyanoacrylate.

The alpha-cyanoacrylates of formula (II) wherein R^3 is a group having the formula $-R^7-\overset{\overset{O}{\|}}{C}-O-R^8$ can be prepared according to the procedure described in U.S. Patent No. 3,995,641 (Kronenthal et al.), which is hereby incorporated by reference. In the Kronenthal et al. method, such alpha-cyanoacrylate monomers are prepared by reacting an alkyl ester of an alpha-cyanoacrylic acid with a cyclic 1,3-diene to form a Diels-Alder adduct which is then subjected to alkaline hydrolysis followed by acidification to form the corresponding alpha-cyanoacrylic acid adduct. The alpha-cyanoacrylic acid adduct is preferably esterified by an alkyl bromoacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct. Alternatively, the alpha-cyanoacrylic acid adduct may be converted to the alpha-cyanoacrylyl halide adduct by reaction with thionyl chloride. The alpha-cyanoacrylyl halide adduct is then reacted with an alkyl hydroxyacetate or a methyl substituted alkyl hydroxyacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct or carbalkoxy alkyl alpha-cyanoacrylate adduct, respectively. The cyclic 1,3-diene blocking group is finally removed and the carbalkoxy methyl alpha-cyanoacrylate adduct or the carbalkoxy alkyl alpha-cyanoacrylate adduct

is converted into the corresponding carbalkoxy alkyl alpha-cyanoacrylate by heating the adduct in the presence of a slight deficit of maleic anhydride.

Examples of monomers of formula (II) include cyanopentadienoates and alpha-cyanoacrylates of the formula:

(III) $CHZ=C\begin{matrix}CN\\ \diagup\\ \diagdown\\ COOR^3\end{matrix}$

wherein Z is $-CH=CH_2$ and R^3 is as defined above. The monomers of formula (III) wherein R^3 is an alkyl group of 1-10 carbon atoms, i.e., the 2-cyanopenta-2,4-dienoic acid esters, can be prepared by reacting an appropriate 2-cyanoacetate with acrolein in the presence of a catalyst such as zinc chloride. This method of preparing 2-cyanopenta-2,4-dienoic acid esters is disclosed, for example, in U.S. Patent No. 3,554,990, which is incorporated by reference herein.

Compositions of this invention comprise an effective amount of a biocompatible pH modifier effective to regulate the pH of an immediate *in situ* environment of the polymer to a pH level at which the polymer's *in vivo* biodegradation proceeds at a different rate than it does at a physiologic pH ("effective amount"). An effective amount of a pH modifier effective to achieve the desired *in situ* pH modification will depend on the acidity or basicity (pKa or pKb) of the compound used, the pH of the polymer composition used when *in situ*, the *in vivo* environment's physiologic pH, and the release rate of biodegradation products resulting from the pH-modified biodegradation rate. An effective amount of pH modifier may be selected with regard to any formaldehyde scavenger or other component added to control levels of biodegradation products released. As well, a non-toxic pH modifier (*e.g.*, an acid) is preferably used, or the pH modifier is used in an effective amount that minimizes any potential toxic effect.

For instance, in embodiments of the invention, a non-encapsulated, acidic pH modifier may be present in an effective amount greater than 1% by weight of the composition. In microencapsulated forms, the amount of pH modifier added may be varied from a minimum effective amount up to a maximum loading permitted by the microcapsule and any toxicity limit, according to the particular monomer or polymer composition and application. At the same time, the pH modifier should not significantly inhibit *in vivo* polymerization of the monomer composition or otherwise interfere with the composition's efficacy for medical or surgical applications.

An acidic or basic pH modifying compound, and its concentration in the composition, may be selected according to the *in vivo* pH range to be achieved in an immediate environment of the *in situ* polymerized or cross-linked adhesive composition. The desired *in situ* pH level depends on the particular monomer or polymer used and on whether that polymer's *in vivo* biodegradation rate is desired to be slower or faster than its biodegradation rate at the physiologic pH of the particular *in vivo* application. One skilled in the biocompatible monomer and polymer field will be able, upon reading this disclosure and with some routine experimentation, to select the pH modifier best suited for a given polymer or monomer composition and the particular application for which it is used.

The pH modifier may be selected to modify, *in vivo*, the pH of an immediate *in situ* environment of the polymer to a pH level at which *in vivo* biodegradation of the *in situ* polymer (and low molecular weight materials in the composition) proceeds more slowly than it does at a physiologic pH. This results in retarding the rate of release of formaldehyde and other degradation products, thereby reducing their toxic effects since, *e.g.*, formaldehyde can be more completely eliminated before substantial, toxic concentrations occur *in situ*.

In such embodiments, the pH modifier may include, for example, but is not limited to, an acidic compound or anhydrous precursor thereof or a chemically protected acid. For example, the pH modifier may comprise at least one member selected from the group consisting of: amino acids; carboxylic acids and salts thereof; di-acids and salts thereof; poly-acids and salts thereof; esters that are easily hydrolyzable *in vivo*; lactones that are easily hydrolyzable *in vivo;* organic carbonates; enolic compounds; acidic phenols; polyphenolic compounds; aromatic alcohols; ammonium compounds or salts thereof; boron-containing compounds; sulfonic acids and salts thereof; sulfinic acids and salts thereof; phosphorus-containing compounds; acid halides; chloroformates; acid gases; acid anhydrides; inorganic acids and salts thereof; and polymers having functional groups of at least one of the preceding members. The pH modifier of this invention may, for example, comprise at least one member selected from the group consisting of: glycine; alanine; proline; lysine; glutaric acid; D-galacturonic acid; succinic acid; lactic acid; glycolic acid; poly(acrylic acid); sodium acetate; diglycolic anhydride; succinic anhydride; citraconic anhydride; maleic anhydride; lactide; diethyl oxalate; Meldrum's acid; diethyl carbonate; dipropyl carbonate; diethyl pyrocarbonate; diallyl pyrocarbonate; di-*tert*-butyl dicarbonate; ascorbic acid; catechin; ammonium chloride; D-glucosamine hydrochloride; 4-hydroxy-ephedrine hydrochloride; boric acid; nitric acid; hydro-chloric acid; sulfuric acid; ethanesulfonic acid; and *p*-toluenesulfonic acid; 2-aminoethylphosphoric acid; methylphosphonic acid; dimethylphosphinic acid; methyl chloroformate; sulfur dioxide; and carbon dioxide. Glutaric acid and diethyl carbonate are particularly preferred in embodiments of the invention.

The pH modifier may alternatively be selected to modify, *in vivo*, a pH of an immediate *in vivo* environment of the polymer to a pH level at which *in vivo* biodegradation of the *in situ* polymer proceeds more

quickly than it does at a physiologic pH. Basic pH modifiers allow the use of polymer materials otherwise degrading slowly or not at all *in vivo*, *e.g.*, butyl alpha-cyanoacrylate or 2-octyl alpha-cyanoacrylate. The pH modifier is added in an amount sufficient to accelerate the polymer's biodegradation, but the accelerated release of biodegradation products (*e.g.*, formaldehyde) must remain within physiologically tolerable ranges. In this aspect, a formaldehyde scavenger may also be added to keep formaldehyde levels within tolerable levels, for instance, in the manner of related application, U.S.S.N. 08/040,618.

In such embodiments, the pH modifier may include a basic compound or anhydrous precursor thereof, and/or a chemically protected base. For example, the pH modifier may comprise at least one member selected from the group consisting of: hydroxides; alkoxides; basic carbonates; nitrogen-containing compounds; amines; alkaloids; hydrides; organolithium compounds; Grignard reagents; carbanions; and polymers having functional groups of at least one of the preceding members. The pH modifier (whether single or in combination) may be, for example, selected from the group consisting of: sodium hydroxide; potassium hydroxide; sodium methoxide; potassium *t*-butoxide; sodium carbonate; calcium carbonate; dibutylamine; tryptamine; sodium hydride; calcium hydride; butyllithium; and ethylmagnesium bromide.

The present invention encompasses situations in which formaldehyde is released as a byproduct of *in situ* biodegradation of the biocompatible polymer. A formaldehyde concentration-reducing agent or formaldehyde scavenger, *e.g.*, sodium bisulfite, may be added to the compositions and methods of this invention to control formaldehyde release *in situ* and to minimize harmful effects therefrom, as disclosed in related application, U.S.S.N. 08/040,618, incorporated herein by reference. However, an acid pH modifier-containing composition herein disclosed can further minimize active formaldehyde concentrations *in situ* in the following manner. The pH

modifier regulates the immediate pH environment of the *in situ* polymerized composition such that the polymer's *in situ* biodegradation is slowed, thereby keeping *in situ* formaldehyde concentrations at a level that can be handled physiologically and that will not, in an initial burst, overwhelm any formaldehyde scavenger that is present.

The pH modifier used in this invention may either be in free form or in a protected form. For instance, it may be in a form that is insoluble in the monomer of a monomer composition, such as a free acid or a microencapsulated form, or may be in a chemically protected form that may be soluble or insoluble in such monomer compositions. Once *in vivo*, the pH modifier may diffuse through the microcapsule or be released by bioerosion of the microcapsule, into the *in situ* polymer. The microcapsule may be formulated so that the pH modifier is released from the microcapsule continuously over a period of time during the biodegradation of the *in situ* polymer. Alternatively, the microencapsulated pH modifier may be formed to release rapidly and transiently, after a time delay, or even intermittently, *vis-à-vis* the life of the *in situ* polymer, depending on when the pH modifier is desired to have effect. For example, delayed release of a basic pH modifier may be desired to cause the polymer to begin to degrade rapidly after it has served a significant portion of its useful life. As well, pH modifiers may be used in combination, allowing, *e.g.*, quick release of an acidic pH modifier followed by later release of a basic pH modifier, for more refined control of the polymer's biodegradation.

For purposes of this invention, the microencapsulated form of the pH modifier is advantageous because this embodiment prevents or substantially reduces pre-application effects of the pH modifier, *e.g.*, a basic pH modifier, thereby increasing shelf-life and facilitating handling of the monomer composition during use.

Microencapsulation of the pH modifier can be achieved by many known microencapsulation techniques. For

example, microencapsulation can be carried out by dissolving a coating polymer in a volatile solvent, e.g., methylene chloride, to a polymer concentration of about 6% by weight; adding a pH modifying compound (selected to be acidic or basic according to the pH level to be achieved *in situ*) in particulate form to the coating polymer/solvent solution under agitation, to yield a pH modifier concentration of 2% to 10% by weight; adding the resulting polymer dispersion to a methylene chloride solution containing a phase inducer, such as silicone oil, under agitation; allowing the mixture to equilibrate for about 20 minutes; further adding the mixture slowly to a non-solvent, such as heptane, under rapid agitation; allowing the more volatile solvent to evaporate under agitation; removing the agitator; separating the solids from the silicone oil and heptane; and washing and drying the microparticles. The size of the microparticles will range from about 0.001 to about 1000 microns.

The microencapsulating coating polymer should be able to undergo *in vivo* bioerosion or to permit diffusion of the pH modifier, and should have low inherent moisture content. Bioerosion preferably occurs at rates greater than or similar to the rate of degradation of the base polymer. Such "bioerosion" can occur as a result of the physical or chemical breakdown of the encapsulating material, for example, by the encapsulating material passing from solid to solute in the presence of body fluids, or by biodegradation of the encapsulating material by agents present in the body.

Examples of coating materials that can be used to microencapsulate the pH modifier include, but are not limited to: polyesters, such as polyglycolic acid, polylactic acid, copolymers of polyglycolic acid and polylactic acid, polycaprolactone, poly-β-hydroxybutyrate, copolymers of ε-caprolactone and δ-valerolactone, copolymers of ε-caprolactone and DL-dilactide, and polyester hydrogels; polyvinylpyrrolidone; polyamides; gelatin; albumin; proteins; collagen; poly(orthoesters);

poly(anhydrides); poly(alkyl-2-cyanoacrylates); poly(dihydropyrans); poly(acetals); poly(phosphazenes); poly(urethanes); poly(dioxinones); cellulose; and starches.

Examples of a phase inducer that can be added include silicone oil, mineral oil, polyethylene, polyisobutylene, and polybutadiene.

Compositions of this invention may further contain a stabilizer and/or one or more adjuvant substances, such as thickening agents, plasticizers, or the like, to improve its medical utility for particular medical applications.

Examples of suitable stabilizers include sulfur dioxide, sulfonic acid, lactone, boron trifluoride, hydroquinone, hydroquinone monomethyl ether, catechol, pyrogallol, benzoquinone, 2-hydroxybenzoquinone, *p*-methoxy phenol, *t*-butyl catechol, organic acid, butylated hydroxy anisole, butylated hydroxy toluene, *t*-butyl hydroquinone, alkyl sulfate, alkyl sulfite, 3-sulfolene, alkylsulfone, alkyl sulfoxide, mercaptan, and alkyl sulfide.

Suitable thickeners include, for example, poly-cyanoacrylates, polylactic acid, polyglycolic acid, lactic-glycolic acid copolymers, polycaprolactone, lactic acid-caprolactone copolymers, poly-3-hydroxybutyric acid, polyorthoesters, polyalkyl acrylates, copolymers of alkylacrylate and vinyl acetate, polyalkyl methacrylates, and copolymers of alkyl methacrylates and butadiene.

Examples of suitable plasticizers include dioctyl phthalate, dimethyl sebacate, triethyl phosphate, tri(2-ethylhexyl)phosphate, tri(*p*-cresyl) phosphate, glyceryl triacetate, glyceryl tributyrate, diethyl sebacate, dioctyl adipate, isopropyl myristate, butyl stearate, lauric acid, dibutyl phthalate, trioctyl trimellitate, and dioctyl glutarate.

To improve the cohesive strength of adhesives formed from the compositions of this invention, difunctional monomeric cross-linking agents may be added to compositions or used in methods of this invention *in vivo*

or *ex vivo*. Such crosslinking agents are known. Reference is made, for example, to U.S. Patent No. 3,940,362 (Overhults), which is hereby incorporated by reference herein. Examples of suitable crosslinking agents include alkyl bis(2-cyanoacrylates), triallyl isocyanurates, alkylene diacrylates, alkylene dimethacrylates, trimethylol propane triacrylate, and alkyl bis(2-cyanoacrylates). When used *ex vivo*, a catalytic amount of a free radical initiator is added to initiate polymerization of the cyanoacrylate monomer/crosslinking agent blend. Such compositions can be molded or otherwise formed to provide preformed implants and prosthetic devices for surgical use, such as rods, meshes, plates, screws, and fasteners.

The compositions of this invention may further contain fibrous reinforcement and colorants, *e.g.*, dyes and pigments. Examples of suitable fibrous reinforcement include PGA microfibrils, collagen microfibrils, cellulosic microfibrils, and olefinic microfibrils. Examples of suitable colorants include 1-hydroxy-4-[4-methylphenylamino]-9,10 anthracenedione (FD&C violet No. 2); disodium salt of 6-hydroxy-5-[(4-sulfophenyl)axo]-2-naphthalenesulfonic acid (FD&C Yellow No. 6); 9-(*o*-carboxyphenyl)-6-hydroxy-2,4,5,7-tetraiodo-3H-xanthen-3-one, disodium salt, monohydrate (FD&C Red No. 3); 2-(1,3-dihydro-3-oxo-5-sulfo-2H-indol-2-ylidene)-2,3-dihydro-3-oxo-1H-indole-5-sulfonic acid disodium salt (FD&C Blue No. 2); and [phthalocyaninato (2-)] copper.

The biocompatible adhesive compositions of this invention can be used, for example, to join together two surfaces, at least one of the surfaces being body or living tissue, by applying the composition to at least one of the surfaces. Depending on the particular requirements of the user, the compositions of this invention can be applied by known means, such as with a glass stirring rod, sterile brush, medicine dropper, spray bottle or other non-aerosol means. However, in many situations, a pressurized aerosol dispensing package is advantageous, in

which the adhesive composition is in solution with a compatible anhydrous or other aerosol propellant. Aerosol application of the monomers is particularly advantageous for use in hemostasis. The compositions of this invention may also be stored in and dispensed from a two-phase container, in which the pH modifier is kept apart from the monomer composition until shortly before or at the moment of applying the adhesive composition *in situ* to the *in vivo* surfaces to be bonded. If a formaldehyde concentration-reducing agent is also present, it may be present in either of the above two phases, or in a separate third phase of a multi-phase container.

In one embodiment, the present invention is directed to a method of joining together *in vivo* two surfaces, one or both of which may be a body tissue, which comprises (a) applying to at least one of said surfaces a biocompatible composition of this invention, and (b) maintaining the surfaces in contact until said composition joins together the two surfaces (*e.g.*, by polymerization of the monomer composition). One of said surfaces can be body tissue and the other surface a prosthetic device or the like, or both surfaces may be body tissue. As one example of a composition which may be used to practice this method, said composition may comprise: (1) at least one monomer (e.g., a monomer of formula (I)) which forms a polymer whose *in vivo* biodegradation proceeds at a physiologic pH (and may release formaldehyde); and (2) an effective amount of a biocompatible pH modifier effective to regulate the pH of an immediate *in situ* environment of the biocompatible polymer to a pH level at which said polymer biodegrades at a different rate than it does at said physiologic pH. The pH modifier may be selected to slow or to accelerate the polymer's biodegradation.

Various methods for repairing or strengthening damaged living tissue to prevent the escape of fluids therethrough exist which may employ a composition of the invention. For example, a method for repairing or dressing living tissue may comprise: (a) applying to the

tissue a surgical sealant comprising the biocompatible composition including a pH modifier of this invention; and (b) allowing the composition to polymerize. A method for stemming the flow of blood from small vessels may comprise applying to said vessels a surgical sealant or hemostatic agent comprising a biocompatible monomer composition including a pH modifier. A method of dressing burns to promote the healing thereof may comprise (a) covering said burn with a biocompatible composition of this invention; and (b) allowing the composition to polymerize *in situ*; and methods of dressing wounds to promote the healing thereof may comprise (a) covering said wound with a biocompatible composition of this invention; and (b) allowing the composition to polymerize.

Repairing injured tissues (for example, to control bleeding) may comprise, for example, sponging to remove superficial body fluids and subsequent application to the exposed tissue of a composition of the invention. For example, a monomer composition polymerizes to a thin film of polymer while in contact with the tissue surface. For bonding separate surfaces of body tissues, the monomer is applied to at least one surface, and the surfaces are brought quickly together while the monomer polymerizes in contact with both surfaces.

In another embodiment, the present invention may be used in a method for effecting *in vivo* administration of a bioactive agent, comprising introducing into a body a composition of this invention, which may comprise: (a) a polymer whose *in vivo* biodegradation may or may not release formaldehyde; (b) an effective amount of a biocompatible pH modifier; and (c) a bioactive amount of a bioactive agent, wherein biodegradation of the polymer or diffusion of the bioactive agent effects its *in vivo* release. The bioactive agent may be encapsulated in a suitable biodegradable material for controlling release of the bioactive agent. The polymer may be one degrading slowly or not at all or may be hydrolytically sensitive, at an *in vivo* physiologic pH. In the former case, a basic

pH modifier may be added to promote biodegradation of the polymer. The composition may also include an effective amount of at least one biocompatible agent effective to reduce active formaldehyde concentration levels, *e.g.*, a formaldehyde scavenger.

The compositions may be used further to administer therapeutic agents into the body. The composition will form a matrix for the therapeutic agent, with the therapeutic agent being released *in vivo* from the matrix by diffusion or by biodegradation, over time, of the polymer. For example, a composition comprising the monomer (or polymer form of the monomer, since in this application, polymerization need not occur *in situ*), a biocompatible pH modifier of this invention, an optional biocompatible formaldehyde scavenger, and a therapeutic agent are introduced into the body where the polymer undergoes biodegradation, gradually releasing the therapeutic agent. Alternatively, the therapeutic agent may diffuse out from the composition, into the body, before polymeric biodegradation ends or even begins.

The monomers are readily polymerized to addition-type polymers and copolymers.

In most bonding applications using compositions of this invention, polymerization of the monomers is catalyzed by small amounts of moisture on the surface of the adherents. Therefore, desired bonding of tissues and hemostasis proceed well in the presence of blood and other body fluids. The bonds formed are of adequate flexibility and strength to withstand normal movement of tissue. In addition, bond strength is maintained as natural tissue healing proceeds concurrently with polymer assimilation.

Compositions employed in the invention are sterilizable by conventional methods such as by autoclave or by aseptic filtration techniques.

The invention is further illustrated by the following non-limiting examples.

EXAMPLES

In the Examples below, the following terms are defined as follows:

IPECA - 2-isopropoxyethyl cyanoacrylate
DMM - dimethyl 2-methylenemalonate
3MBCA - 3-methoxybutyl cyanoacrylate
20CA - 2-octyl cyanoacrylate
monomer(s) - refers generically to IPECA, DMM, 3MBCA and/or 20CA

Examples 1-18 and Control Examples 1C-18C

Examples 1-18 and Control Examples 1C-18C illustrate the effect of a biocompatible pH modifier on the biodegradation of a 1,1-disubstituted ethylene monomer polymerized *in situ*. The compositions of Examples 1-18 each contain a pH modifier (in free or microencapsulated form) while the compositions of Control Examples 1C-18C contain sodium chloride (NaCl), polycaprolactone microcapsules, or no additive.

The formulations of the compositions prepared in Examples 1-18 and Control Examples 1C-18C are shown in Tables IA and IB, respectively.

The compositions of the examples are prepared as follows. Appropriate weight ratios of the monomer and an additive are mixed thoroughly by shaking. (Solid pH modifiers and sodium chloride are ground or milled to a fine particle size before mixing.) The resulting mixture is quickly poured onto a glass plate equipped with a 4 cm x 8 cm boundary. The glass plate is pre-treated with chlorotrimethylsilane and the boundary is fabricated with caulking cord material. The mixture is spread evenly to all edges. Polymerization of the monomer mixture is then accelerated by spraying with a 1% aqueous sodium bicarbonate solution (Examples 1-3, 5, 9-18, 1C-3C, 5C, and 9C-18C) or a 1:2:97 triethylamine/methanol/heptane mixture (Examples 4, 6-8, 4C, and 6C-8C). The hardened polymer film is gently scraped off the glass plate, cut away from the boundary and dried. It is further cut into two halves, each of 2 cm x 8 cm, for duplicate runs.

In Examples 13-15, the additive is sprinkled evenly on the glass plate and the monomer is then carefully added, instead of the two being mixed directly.

In vitro biodegradation (simulating *in vivo* biodegradation) of each 2 cm x 8 cm polymer film is then carried out as follows. The polymer film, encaged in aluminum mesh, is placed in a pH 7.4 buffer (*e.g.*, monobasic potassium phosphate and dipotassium phosphate). Biodegradation is carried out at 37±2°C for 168 hours (Examples 1-9, 13-18, 1C-9C, and 13C-18C) or at 37±2°C for 192 hours (Examples 10-12, and 10C-12C). The partially degraded film is separated from the buffer solution and dried. The buffer solution is subjected to formaldehyde determination.

Determination of the amount of formaldehyde generated during biodegradation of the polymer films may be accomplished as disclosed in related application U.S.S.N. 08/040,618 (U.S. Patent 5,328,687).

In the following tables, the term "μg formaldehyde detected per g polymer" means the amount of formaldehyde generated in micrograms divided by the original polymer weight in grams (excluding the weight of the pH modifier or control additive).

Table IA

Examples 1-18

Example No.	Monomer	Additive	Additive Weight %	µg Formaldehyde Detected per g Polymer	% Change of Formaldehyde Detected
1	IPECA	diethyl carbonate	2.5	1652	- 77.4
2	IPECA	diethyl carbonate	5.0	1278	- 87.0
3	IPECA	diethyl carbonate	7.5	8806	- 14.4
4	IPECA	lactide	7.0	1161	- 73.3
5	IPECA	glucosamine hydrochloride	9.0	6082	- 19.9
6	IPECA	ascorbic acid	2.0	5226	- 66.7
7	IPECA	glutaric acid	1.0	13,788	- 7.3
8	IPECA	glutaric acid/ polycaprolactone microcapsules	8.0	3023	- 20.0
9	3MBCA	glycine	8.0	1909	- 8.7
10	DMM	diethyl oxalate	6.0	1723	- 61.4
11	DMM	tryptamine	3.0	2538	+ 22.6
12	DMM	potassium carbonate	2.0	2372	+ 16.2
13	IPECA	tryptamine/polycapro-lactone microcapsules	4.0	10,376	+ 53.4
14	IPECA	tryptamine/polycapro-lactone microcapsules	6.0	9961	+ 63.7
15	IPECA	tryptamine/polycapro-lactone microcapsules	8.0	9094	+ 46.9
16	IPECA	sodium carbonate/poly-caprolactone microcapsules	10.0	6949	+ 63.6
17	3MBCA	sodium methoxide	5.0	4389	+856.2
18	2OCA	sodium hydroxide	8.5	2351	+1379.0

Table IB

Control Examples 1C-18C

Example No.	Monomer	Additive	Additive Weight %	µg Formaldehyde Detected per g Polymer	% Change of Formaldehyde Detected
1C	IPECA	sodium chloride	2.5	7295	0
2C	IPECA	sodium chloride	5.0	9856	0
3C	IPECA	sodium chloride	7.5	10,293	0
4C	IPECA	sodium chloride	7.0	4355	0
5C	IPECA	sodium chloride	9.0	7595	0
6C	IPECA	sodium chloride	2.0	15,698	0
7C	IPECA	sodium chloride	1.0	14,880	0
8C	IPECA	sodium chloride	8.0	3780	0
9C	3MBCA	sodium chloride	8.0	2091	0
10C	DMM	sodium chloride	6.0	4466	0
11C	DMM	sodium chloride	3.0	2070	0
12C	DMM	sodium chloride	2.0	2041	0
13C	IPECA	polycaprolactone microcapsules	4.0	6764	0
14C	IPECA	polycaprolactone microcapsules	6.0	6085	0
15C	IPECA	polycaprolactone microcapsules	8.0	6189	0
16C	IPECA	polycaprolactone microcapsules	10.0	4248	0
17C	3MBCA	none	0	459	0
18C	20CA	none	0	159	0

The monomer IPECA is polymerized by azoisobutyronitrile (AIBN) at 70°C to give a polymer of approximately 25,000 molecular weight. In the following Examples, polymer(s) refers generically to the IPECA polymer prepared in this manner.

Examples 19-20 and Control Examples 19C-20C

Examples 19-20 and Control Examples 19C-20C illustrate the effect of a biocompatible pH modifier on the biodegradation of a 1,1-disubstituted ethylene polymer. The compositions of Examples 19-20 each contain a pH modifier while the compositions of Control Examples 19C-20C contain sodium chloride (NaCl).

The formulations of the compositions prepared in Examples 19-20 and Control Examples 19C-20C are shown in Table II.

The compositions of the examples are prepared as follows. The polymer is dissolved in methylene chloride to give a polymer concentration of about 15%. The resulting polymer solution and an additive (either a pH modifier or sodium chloride) are mixed thoroughly in the appropriate weight ratio by shaking. (Solid pH modifiers and sodium chloride are ground or milled to a fine particle size before mixing.) The resulting mixture is quickly poured onto a glass plate equipped with a 4 cm x 8 cm boundary. The glass plate is pre-treated with chlorotrimethylsilane and the boundary is fabricated with caulking cord material. The inside border is painted with melted paraffin wax. The mixture is spread evenly to all edges. Following evaporation of solvent, the polymer film is gently scraped off the glass plate, cut away from the boundary and dried. It is further cut into two halves, each of 2 cm x 8 cm, for duplicate runs.

In vitro biodegradation (simulating *in vivo* biodegradation) of the polymer films and formaldehyde determination are carried out using the same procedures followed in Examples 1-9 and 13-18 and Control Examples 1C-9C and 13C-18C. The results of Examples 19-20 and Control Examples 19C-20C are shown in Table II.

Table II

Examples 19-20 and Control Examples 19C-20C

Example No.	Polymer	Additive	Additive Weight %	µg Formaldehyde Detected per g Polymer	% Change of Formaldehyde Detected
19	IPECA	hydrochloric acid	1.0	329	-37.0
20	IPECA	methylphosphonic acid	5.0	906	-55.1
19C	IPECA	sodium chloride	1.0	522	0
20C	IPECA	sodium chloride	5.0	2018	0

We claim:

1. A method comprising:

(a) applying to an *in vivo* surface a biocompatible composition comprising: (1) at least one monomer which forms a polymer *in situ* at a physiologic pH; and (2) an effective amount of at least one biocompatible pH modifier effective to modify the pH of an immediate *in vivo* environment of said polymer to a pH range at which said polymer biodegrades at a different rate than it does at physiologic pH, without said pH modifier significantly affecting the monomer's polymerization *in situ*;

(b) allowing the monomer composition to polymerize *in situ*.

2. The method of claim 1, wherein said composition is an adhesive composition, and said surface is maintained in contact with another surface *in vivo* until the monomer composition polymerizes.

3. The method of claim 2, wherein one of the surfaces is body tissue and the other surface is a prosthetic device.

4. The method of claim 2, wherein both surfaces are body tissue.

5. The method of claim 1, wherein said composition is applied to damaged or exposed tissue.

6. The method of claim 5, wherein said tissue comprises a blood vessel, and said method stems flow of blood from said blood vessel by applying to said blood vessel a hemostatic agent comprising said composition.

7. The method of claim 5, wherein said tissue has been burned or is living tissue exposed in a wound.

8. The method of claim 1, wherein the effective amount of a non-encapsulated, acidic pH modifier is at least 1 % by weight of the composition.

9. The method of claim 1, wherein the pH modifier is soluble in the monomer.

10. The method of claim 1, wherein the polymer's *in vivo* biodegradation proceeds faster than it does at physiologic pH.

11. The method of claim 1, wherein the polymer's *in vivo* biodegradation proceeds slower than it does at physiologic pH.

12. The method of claim 1, wherein the polymer degrades slowly or not at all at a physiologic pH and the pH modifier is a basic compound.

13. The method of claim 1, wherein the polymer comprises at least one member selected from the group consisting of butyl alpha-cyanoacrylate and octyl alpha-cyanoacrylate, and said pH modifier is a basic compound.

14. The method of claim 1, wherein the composition further comprises: (3) at least one biocompatible agent effective to reduce active formaldehyde concentration levels.

15. The method of claim 10, wherein the composition further comprises: (3) at least one biocompatible agent effective to reduce active formaldehyde concentration levels.

16. The method of claim 1, wherein the monomer is an alpha-cyanoacrylate or a 2-methylene malonate.

17. The method of claim 16, wherein the alpha-cyanoacrylate is methyl cyanoacrylate, butyl cyano-acrylate, 2-octyl cyanoacrylate, 1-methoxy-2-propyl cyanoacrylate, 2-butoxyethyl cyanoacrylate, 2-isopropoxy-ethyl cyanoacrylate or 3-methoxybutyl cyanoacrylate.

18. The method of claim 1, wherein the pH modifier is microencapsulated in a material that has a low inherent moisture content and that undergoes *in vivo* bioerosion.

19. The method of claim 1, wherein the pH modifier is microencapsulated in a material and is capable, *in vivo*, of diffusing through the material.

20. The method of claim 1, wherein the pH modifier comprises at least one member selected from the group consisting of:

amino acids;
carboxylic acids or salts thereof;
di-acids or salts thereof;
poly acids or salts thereof;
esters that are easily hydrolyzable *in vivo*;
lactones that are easily hydrolyzable *in vivo*;
organic carbonates;
enolic compounds;
acidic phenols;
polyphenolic compounds;
aromatic alcohols;
ammonium compounds or salts thereof;
boron-containing compounds;
sulfonic acids or salts thereof;
sulfinic acids or salts thereof;
phosphorus-containing compounds;
acid halides;
chloroformates;
acid gases;
acid anhydrides;
inorganic acids or salts;
chemically protected acids; and
polymers having functional groups of at least one of the preceding members.

21. The method of claim 1, wherein the pH modifier comprises at least one member selected from the group consisting of: glycine; alanine; proline; lysine; glutaric acid; D-galacturonic acid; succinic acid; lactic acid; glycolic acid; poly(acrylic acid); sodium acetate; diglycolic anhydride; succinic anhydride; citraconic anhydride; maleic anhydride; lactide; diethyl oxalate; Meldrum's acid; diethyl carbonate; dipropyl carbonate; diethyl pyrocarbonate; diallyl pyrocarbonate; di-tert-butyl dicarbonate; ascorbic acid; catechin; ammonium chloride; D-glucosamine hydrochloride; 4-hydroxyephedrine hydrochloride; boric acid; nitric acid; hydrochloric acid; sulfuric acid; ethanesulfonic acid; *p*-toluenesulfonic

acid; 2-aminoethylphosphoric acid; methylphosphonic acid; dimethylphosphinic acid; and methyl chloroformate.

22. The method of claim 1, wherein the pH modifier comprises at least one member selected from the group consisting of:

hydroxides;
alkoxides;
basic carbonates;
nitrogen-containing compounds;
amines;
alkaloids;
hydrides;
organolithium compounds;
Grignard reagents;
carbanions; and
chemically protected bases; and
polymers having functional groups of at least one of the preceding members.

23. The method of claim 1, wherein the pH modifier comprises at least one member selected from the group consisting of: sodium hydroxide; potassium hydroxide; sodium methoxide; potassium *t*-butoxide; sodium carbonate; dibutylamine; tryptamine; sodium hydride; calcium hydride; butyllithium; and ethylmagnesium bromide.

24. A method of regulating a rate of *in vivo* biodegradation of a polymer formed *in vivo* from at least one monomer which forms a polymer at a physiologic pH, comprising:

combining said at least one monomer with an effective amount of at least one biocompatible pH modifier effective to modify a pH of an immediate *in situ* environment of the polymer to a pH range at which the polymer's biodegradation proceeds at a different rate than it does at physiologic pH;

allowing the polymer to form *in vivo*; and

maintaining the thus-formed polymer *in vivo* for a time sufficient to effect biodegradation of the polymer.

25. The method of claim 24, wherein the polymer is a 1,1-disubstituted ethylene.

26. The method of claim 24, wherein the polymer is hydrolytically sensitive *in vivo* at a physiologic pH.

27. The method of claim 24, wherein the polymer biodegrades slowly or not at all at a physiologic pH, and the pH modifier is a basic compound.

28. The method of claim 24, wherein the polymer comprises at least one member selected from the group consisting of butyl alpha-cyanoacrylate and octyl alpha-cyanoacrylate, and said pH modifier is a basic compound.

29. A biocompatible monomer composition, comprising:

a) at least one monomer comprised of a 1,1-disubstituted ethylene, which forms a polymer *in vivo* at a physiologic pH; and

b) an effective amount of a biocompatible pH modifier effective to regulate, after *in vivo* polymerization of the monomer *in situ*, the pH of an immediate *in vivo* environment of the polymer to a pH range at which the polymer biodegrades *in vivo* at a different rate than it does at physiologic pH, without significantly affecting *in situ* polymerization of the monomer.

30. The composition of claim 29, wherein the polymer biodegrades *in vivo* at physiologic pH.

31. The composition of claim 29, wherein the pH modifier is in a form that is substantially insoluble in the monomer.

32. The composition of claim 29, wherein the pH modifier is soluble in the monomer.

33. The composition of claim 29, wherein the pH modifier is microencapsulated in a coating polymer that has a low inherent moisture content and that undergoes *in vivo* bioerosion.

34. The composition of claim 33, wherein the pH modifier is capable, *in vivo*, of diffusing through the coating polymer.

35. The composition of claim 29, wherein the pH modifier is effective to promote a faster *in vivo* biodegradation of the polymer than that occurring at physiologic pH.

36. The composition of claim 29, wherein the pH modifier is effective to promote a slower *in vivo* biodegradation of the polymer than that occurring at physiologic pH.

37. The composition of claim 29, wherein a non-encapsulated acidic pH modifier comprises at least about 1% by weight of the composition.

38. The composition of claim 29, wherein the at least one monomer is an alpha-cyanoacrylate or a 2-methylene malonate.

39. The composition of claim 37, wherein the alpha-cyanoacrylate is methyl cyanoacrylate, butyl cyanoacrylate, 2-octyl cyanoacrylate, 1-methoxy-2-propyl cyanoacrylate, 2-butoxyethyl cyanoacrylate, or 2-iso-propoxyethyl cyanoacrylate or 3-methoxybutyl cyanoacrylate.

40. The composition of claim 29, further comprising an effective amount of at least one biocompatible agent effective to reduce active formaldehyde concentration levels.

41. The composition of claim 29, wherein the pH modifier is a chemically protected acid or an acid or anhydrous precursor thereof.

42. The composition of claim 29, wherein the pH modifier comprises at least one member selected from the group consisting of:

amino acids;
carboxylic acids or salts thereof;
di-acids or salts thereof;
poly acids or salts thereof;
esters that are easily hydrolyzable *in vivo*;
lactones that are easily hydrolyzable *in vivo*;
organic carbonates;
enolic compounds;

acidic phenols;
polyphenolic compounds;
aromatic alcohols;
ammonium compounds or salts thereof;
boron-containing compounds;
sulfonic acids or salts thereof;
sulfinic acids or salts thereof;
phosphorus-containing compounds;
acid halides;
chloroformates;
acid gases;
acid anhydrides;
inorganic acids or salts; and
polymers having functional groups of at least one of the preceding members.

43. The composition of claim 29, wherein the pH modifier comprises at least one member selected from the group consisting of: glycine; alanine; proline; lysine; glutaric acid; D-galacturonic acid; succinic acid; lactic acid; glycolic acid; poly(acrylic acid); sodium acetate; diglycolic anhydride; succinic anhydride; citraconic anhydride; maleic anhydride; lactide; diethyl oxalate; Meldrum's acid; diethyl carbonate; dipropyl carbonate; diethyl pyrocarbonate; diallyl pyrocarbonate; di-*tert*-butyl dicarbonate; ascorbic acid; catechin; ammonium chloride; D-glucosamine hydrochloride; 4-hydroxyephedrine hydrochloride; boric acid; nitric acid; hydrochloric acid; sulfuric acid; ethanesulfonic acid; p-toluenesulfonic acid; 2-aminoethylphosphoric acid; methylphosphonic acid; dimethylphosphinic acid; and methyl chloroformate.

44. The composition of claim 29, wherein the pH modifier is a chemically protected base or a base or anhydrous precursor thereof.

45. The composition of claim 29, wherein the pH modifier comprises at least one member selected from the group consisting of:

hydroxides;
alkoxides;

basic carbonates;
nitrogen-containing compounds;
amines;
alkaloids;
hydrides;
organolithium compounds;
Grignard reagents;
carbanions; and
polymers having functional groups of at least one of the preceding members.

46. The composition of claim 29, wherein the pH modifier comprises at least one member selected from the group consisting of: sodium hydroxide; potassium hydroxide; sodium methoxide; potassium *t*-butoxide; sodium carbonate; dibutylamine; tryptamine; sodium hydride; calcium hydride; butyllithium; and ethylmagnesium bromide.

47. The composition of claim 29, wherein the polymer biodegrades slowly or not at all at physiologic pH.

48. The composition of claim 47, wherein the polymer comprises at least one member selected from the group consisting of butyl alpha-cyanoacrylate and octyl alpha-cyanoacrylate.

49. The composition of claim 47, further comprising an effective amount of at least one biocompatible agent effective to reduce active formaldehyde concentration levels.

50. A surgical adhesive comprising the composition of claim 29.

51. A surgical sealant comprising the composition of claim 29.

52. A method of joining together two surfaces *in vivo*, at least one of the surfaces being body tissue, which comprises applying to at least one of the surfaces a composition of claim 29 and maintaining the surfaces in contact until said composition polymerizes *in situ*.

53. A biocompatible composition, comprising:

(a) a polymer whose *in vivo* biodegradation produces formaldehyde; and

(b) an effective amount of at least one biocompatible pH modifier effective to modify the pH of an immediate environment of the biocompatible composition *in situ* to a pH range at which the polymer's *in situ* biodegradation proceeds at a rate different than at physiologic pH.

54. The composition of claim 53, wherein the pH modifier is an acid or anhydrous precursor thereof or a chemically protected acid.

55. The composition of claim 53, wherein the pH modifier is a base or anhydrous precursor thereof or a chemically protected base.

56. The composition of claim 53, wherein the polymer is formed *in vivo*.

57. The composition of claim 53, wherein the polymer is formed *ex vivo*.

58. The composition of claim 53, wherein the polymer can biodegrade at a physiologic pH and the pH modifier is an acid or anhydrous precursor thereof or a chemically protected acid.

59. The composition of claim 53, wherein the polymer biodegrades slowly or not at all at physiologic pH and the pH modifier is a base or anhydrous precursor thereof or a chemically protected base.

60. The composition of claim 53, further comprising at least one biocompatible agent effective to reduce active formaldehyde concentration levels.

61. A delivery system for a therapeutic agent, comprising:

(a) a suitable carrier or matrix comprising the composition of claim 53; and

(b) a therapeutic agent deposited on or within the carrier or matrix.

62. A surgical implant molded from the composition of claim 53.

63. The implant of claim 62, comprising a prosthetic device.

64. The implant of claim 63, comprising a tissue fastener.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/08162

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C09J 4/00
US CL :156/331.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 156/331.2; 427/2.1; 526/298; 523/118; 604/214; 424/78.06, 78.35, 487

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A, 3,559,652 (BANITT ET AL) 02 February 1971 See Abstract, col. 1 lines 3-4 and 15-69, col 2 line 67 thru col. 3 line 73, col. 4 lines 10-26	1-7, 9-10, 12-19, 22-35, 38-40, 44-53, 55-57, 59-61
Y	US,A, 3,527,841 (WICKER ET AL) 08 September 1970 See Abstract, col. 1 lines 25-35, col 2 lines 4-13 and 40-72, col. 3 lines 1-21	1-7, 9-10, 12-19, 22-35, 38-40, 44-53, 55-57, 59-61
Y	US,A, 3,483,870 (COOVER ET AL) 16 December 1969 See Abstract, col. 1 lines 66-72, col. 2 lines 7-19, col. 4 lines 10-13 and 53-75, col. 5 lines 27-48	1-7, 9-10, 12-19, 22-35, 38-40, 44-53, 55-57, 59-61

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
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Date of the actual completion of the international search 04 AUGUST 1995	Date of mailing of the international search report 02OCT1995
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INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A, 5,302,628 (LIM ET AL) 12 April 1994 See Abstract, col. 4 lines 25-33 and 44-55	1-7, 9-10, 12-19, 22-35, 38-40, 44-53, 55-57, 59-61
Y	US,A, 4,479,933 (AKIMOVA ET AL) 30 October 1984 See col. 1 lines 15-49	1-7, 9-10, 12-19, 22-35, 38-40, 44-53, 55-57, 59-61
Y	US,A, 4,196,271 (YAMADA ET AL) 01 April 1980 See Abstract, col. 1 lines 46-57, col. 2 lines 65 thru col. 3 line 36	1-9, 11, 14-21, 24-26, 29-34, 36-43, 47-54, 56-68, 60-61